For at least 60 years, surgical resection has been a widely used approach to the management of patients with lung metastases from a variety of solid tumors. For many of these patients, surgical resection has provided the only potentially curative treatment. Analyses of numerous retrospective series have led to well-accepted surgical selection criteria: a primary tumor that has been definitively controlled, metastases limited to the lung that can be completely resected, ability of the patient to tolerate the planned operation, and lack of a better alternative treatment. The number of lung metastases, the disease-free interval since treatment of the primary tumor, the tumor doubling time, the presence of lymph node metastases, the histology of the primary tumor, and in some instances, elevated serum markers such as carcinoembryonic antigen are known to influence outcome and may be incorporated into the decision of whether to offer surgery to the patient. However, there remain many controversial aspects to pulmonary metastasectomy, which are the subject of a thoughtful review by members of the European Society of Thoracic Surgeons in this issue of the Journal of Thoracic Oncology. We lack definitive data on issues such as the optimal preoperative imaging studies, when mediastinal nodal staging should be performed before or during resection, whether a minimally surgical approach (video-assisted thoracic surgery) allows adequate resection, under what circumstances reoperative pulmonary metastasectomy is appropriate, how pulmonary metastasectomy should be integrated with other treatments, and whether other local therapies such as radiofrequency ablation or stereotactic radiotherapy offer equivalent results.1–11

The management of patients with a previously treated malignancy is further confounded by the fact that the development of one or more new pulmonary nodules does not always represent metastatic disease. Early surgical series reported that approximately 5% of new lung nodules in patients previously treated for breast and colon cancer proved to be benign and up to half were found to be primary lung carcinomas.12–14 The likelihood that a new lung nodule is a metastasis as opposed to a second primary cancer is influenced by the type of original malignancy. In patients whose initial cancer was a sarcoma or melanoma, a new pulmonary nodule is approximately 10 times more likely to be a metastasis than a second primary cancer. If the original primary tumor was a genitourinary or colorectal cancer, there is approximately 50% chance that the new nodule is a metastasis. If the original tumor was a head and neck cancer, the new nodule is twice as likely to be a new primary lung cancer than a metastasis. These findings are likely related to tobacco exposure being the common etiology for primary malignancies in multiple sites.15 Before assuming that a patient has metastatic and potentially incurable disease, it is important to establish a tissue diagnosis, either intraoperatively or before initiating nonsurgical treatment. Fine needle aspiration may yield sufficient tissue to distinguish between some primary tumors (e.g., colon metastasis versus new lung adenocarcinoma), but the pathologic differential diagnosis can be problematic for other tumors (e.g., metastatic breast versus primary lung adenocarcinoma) and may require more tissue. Distinguishing between metastatic head and neck cancer and primary lung squamous cell carcinomas is particularly difficult because squamous cell carcinomas from multiple sites can appear morphologically identical to one another. Molecular analyses, when available, may assist in this regard as can the clinical scenario (e.g., disease-free interval since treatment of primary tumor). Establishing a definitive tissue diagnosis is especially important when considering nonsurgical local treatment modalities such as radiofrequency ablation, stereotactic radiotherapy, or systemic therapy. It is also critical to the design of clinical trials in this patient population.

The history of pulmonary metastasectomy indicates that it is a moving target—a procedure for which the indications are constantly evolving. In the era before effective chemotherapy, pulmonary metastasectomy series included large numbers of patients with osteogenic sarcoma and breast cancer.17,18 These patients are now treated predominantly with systemic therapy with only highly selected patients considered for surgical resection.19 The advent of effective chemotherapy for germ cell tumors changed pulmonary metastasectomy from being a primary intervention to an adjuvant treatment directed at detection and resection of minimal residual cancer and removal of benign teratoma.20 A similar evolution is now occurring in the management of metastatic...
colorectal and renal cancers. For decades, when there was little effective systemic therapy for colorectal cancer, surgeons carefully redefined the indications for pulmonary metastasectomy in these patients.\textsuperscript{21,22} However, during the past decade, the development of new effective chemotherapy and of targeted therapies has radically altered the management of patients with metastatic colorectal cancer. Resection of a solitary metastasis in a patient with indolent disease, a normal carcinoembryonic antigen, and no lymph node metastases may still be the best approach, but how to integrate surgery into the treatment of the majority of patients with colorectal cancer and lung metastases is now undefined. Should we treat them with systemic therapy only, administer chemotherapy as induction or adjuvant treatment after pulmonary metastasectomy, or “sandwich” surgery within a chemotherapy program? The development of antiangiogenesis agents is rapidly altering the management of patient with renal cell cancer. Although pulmonary metastasectomy used to be the most effective treatment for many of these patients, this is no longer the case. When to perform pulmonary metastasectomy in such cases is an open question.

Clearly, there is a need for prospective clinical trials in patients being considered for pulmonary metastasectomy. Some questions, such as the optimal approach to preoperative imaging or the validity of minimally invasive surgery, would be fairly straightforward to ask and answer. Because the number of patients who are candidates for pulmonary metastasectomy in any single institution is relatively small, such trials would be best performed in a multicenter setting. The question of therapeutic benefit, especially in patients for whom effective chemotherapy now exists, is much harder to answer. The planned randomized trial described by Tom Treasure in this issue of the Journal of Thoracic Oncology is an ambitious effort to define optimal treatment for patients with metastatic colorectal cancer. In the era of both rapidly evolving molecular medicine and technology, it can be increasingly difficult to perform randomized controlled trials that attempt to determine the benefit of surgical resection. Such trials require many years to develop and perform. During the past decade, we have repeatedly seen that the discovery of a single critical molecular abnormality and the development of therapies directed to that abnormality can revolutionize, almost overnight, the treatment of a malignancy. Witness, for example, the recent changes in treatment that have occurred in the treatment of chronic myelogenous leukemia, gastrointestinal stromal tumors, epidermal growth factor receptor-mutant lung adenocarcinomas, breast cancer, colon cancer, and renal cell cancer. Major technological improvements in radiotherapy and ablative therapies also have the potential to alter the indications for surgery or render surgical intervention obsolete. There are many important questions that need to be answered in patients thought to be candidates for pulmonary metastasectomy.

Selecting the best questions and designing the clinical trials that could lead to durable results is the big challenge. The members of the European Society of Thoracic Surgeons deserve credit for assessing our current state of knowledge about pulmonary metastasectomy in a way that could frame future clinical trials.

REFERENCES